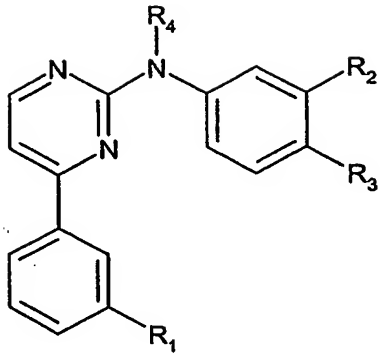
Patent Claims

1. A compound of formula



I

wherein

R_1 is halogen or halo(C_{1-4})alkyl,

R_2 is hydrogen, halogen or halo(C_{1-4})alkyl,

R_3 is halogen or halo(C_{1-4})alkyl,

R_4 is hydrogen, (C_{1-8})alkyl, hydroxy(C_{1-6})alkyl or a group of formula

-CO-R_5,

-CO-$(CH_2)_m$-OR_6,

-CO-CO-R_7,

-CO-CO-OR_8,

-CO-N(R_9R_{10}),

-CO-$(CH_2)_n$-CO-R_{11},

-CO-(CHR_{15})-O-$(CH_2)_o$-CO-R_{11},

-CO-$(CH_2)_p$-O-$(CH_2)_q$-O-$(CH_2)_r$-R_{16},

-CO-O-$(CH_2)_s$-O-CO-R_{17},

-CO-O-$(CH_2)_t$-N($R_{18}R_{19}$),

-CO-O-$(CH_2)_u$-NH-CO-CH(NH_2)-R_{20}, or

-CO-O-$(CH_2)_w$-NH-CO-R_{17}, wherein

R_5 is hydrogen, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, amino, (C_{1-4})alkylamino, di(C_{1-4})alkylamino, aryl or heterocyclyl which is a 5 or 6-membered heterocyclic ring system having 1 to 4 heteroatoms selected from N, O or S,

R_6 is hydrogen, (C_{1-4})alkyl, (C_{3-8})cycloalkyl, aryl, (C_{1-4})alkyl substituted by heterocyclyl which is a 5 or 6-membered heterocyclic ring system having 1 to 4 heteroatoms selected from N, O or S, amino(C_{1-6})alkyl, (C_{1-4})alkylamino(C_{1-6})alkyl, di(C_{1-4})alkylamino(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, hydroxy(C_{1-4})alkylamino(C_{1-6})alkyl or an amino acid residue,

e.g. $-CH_2-CH(NH_2)-COOH$,

R_7 and R_8 independently of each other are (C_{1-4})alkyl, (C_{3-8})cycloalkyl, aryl or heterocyclyl which is a 5 or 6-membered heterocyclic ring system having 1 to 4 heteroatoms selected from N, O or S,

R_9 and R_{10} independently of each other are hydrogen or (C_{1-4})alkyl or one of R_9 and R_{10} is hydrogen and the other is (C_{3-8})cycloalkyl, (C_{1-4})alkyl, aryl or heterocyclyl,

R_{11} is (C_{1-4})alkyl, $-OR_{12}$, $-NR_{13}R_{14}$, an amino acid, an (C_{1-4})alkylester thereof or a di(C_{1-4})alkylester thereof ,

R_{12} is hydrogen or (C_{1-4})alkyl,

R_{13} and R_{14} independently of each other are hydrogen, (C_{1-4})alkyl, amino(C_{1-6})alkyl, (C_{1-4})alkylamino(C_{1-6})alkyl, di(C_{1-4})alkylamino(C_{1-6})alkyl,

R_{15} is hydrogen or (C_{1-4})alkyl,

R_{16} is hydrogen, (C_{1-4})alkyl, carboxyl or carboxylic ester,

R_{17} is amino(C_{1-4})alkyl, (C_{1-4})alkylamino(C_{1-4})alkyl or di(C_{1-4})alkylamino(C_{1-4})alkyl,

R_{18} is hydrogen or (C_{1-4})alkyl,

R_{19} is hydroxy(C_{1-4})alkyl,

R_{20} is (C_{1-4})alkyl or hydroxy(C_{1-4})alkyl,

m is 0 to 4,

n is 2 to 8,

o is 0 to 4,

p is 0 to 4,

q is 1 to 8,

r is 0 to 4,

s is 1 to 4,

t is 1 to 4,

u is 1 to 6 and

w is 1 to 6.

2. A compound of claim 1 wherein

- R_1 is chloro or trifluoromethyl,
- R_2 is hydrogen or trifluoromethyl,
- R_3 is chloro, fluoro or trifluoromethyl,
- R_4 is hydrogen, (C_{1-4})alkyl, e.g. methyl, hydroxy(C_{1-4})alkyl, e.g.hydroxyethyl, or a group of formula

$-CO-R_5$,

$-CO-(CH_2)_m-OR_6$,

$-CO-CO-R_7$,

$-CO-CO-OR_8$,

$-CO-N(R_9R_{10})$,

$-CO-(CH_2)_n-CO-R_{11}$,

$-CO-(CHR_{15})-O-(CH_2)_o-CO-R_{11}$,

$-CO-(CH_2)_p-O-(CH_2)_q-O-(CH_2)_r-R_{16}$,

$-CO-O-(CH_2)_s-O-CO-R_{17}$,

$-CO-O-(CH_2)_t-N(R_{18}R_{19})$,

$-CO-O-(CH_2)_u-NH-CO-CH(NH_2)-R_{20}$, or

$-CO-O-(CH_2)_w-NH-CO-R_{17}$, wherein

R_5 is hydrogen, (C_{1-4})alkyl, (C_{3-6})cycloalkyl, dimethylamino, phenyl or heterocyclyl which is a 6-membered heterocyclic ring system having one O as a heteroatom, e.g. tetrahydropyranyl,

R_6 is hydrogen, (C_{1-4})alkyl, (C_{1-2})alkyl substituted by heterocyclyl which is a 5 or 6-membered heterocyclic ring system having 1 or 2 heteroatoms selected from N or O, e.g. including unsubstituted pyrrolidine, morpholine and piperazine and piperazine substituted by e.g. (C_{1-2})alkyl or (C_{1-2})hydroxyalkyl; amino(C_{1-4})alkyl, (C_{1-2})alkylamino(C_{1-4})alkyl, di(C_{1-2})alkylamino(C_{1-4})alkyl, hydroxy(C_{1-3})alkyl, hydroxy(C_{1-2})alkylamino(C_{1-2})alkyl or an amino acid residue, e.g. $-CH_2-CH(NH_2)-COOH$,

R_7 and R_8 independently of each other are (C_{1-2})alkyl or phenyl,

R_9 and R_{10} independently of each other are hydrogen or (C_{1-2})alkyl,

R_{11} is (C_{1-2})alkyl, $-OR_{12}$, $-NR_{13}R_{14}$, an amino acid, an (C_{1-2})alkylester thereof or an di(C_{1-2})alkylester thereof, preferably an amino acid selected from the group consisting of alanine, phenylalanine, glutamic acid and lysine, wherein the binding is effected via the α- amino group or in the case of e.g. lysine via the ε-amino group,

R_{12} is hydrogen or (C_{1-2})alkyl,

R_{13} and R_{14} independently of each other are hydrogen, (C_{1-2})alkyl, amino(C_{1-4})alkyl, (C_{1-2})alkylamino(C_{1-4})alkyl, di(C_{1-2})alkylamino(C_{1-4})alkyl,

R_{15} is hydrogen or (C_{1-2})alkyl,

R_{16} is hydrogen, (C_{1-2})alkyl, carboxyl or carboxylic ester,

R_{17} is amino(C_{1-2})alkyl,

R_{18} is hydrogen or (C_{1-2})alkyl,

R_{19} is hydroxy(C_{1-2})alkyl,

R_{20} is (C_{1-2})alkyl or hydroxy(C_{1-2})alkyl,
m is 0 or 1,
n is 2 to 4,
o is 0 or 1,
p is 0 to 2,
q is 2 to 5,
r is 0 to 2,
s is 2,
t is 2,
u is 1 to 3 and
w is 1 to 3.

3. A compound according to claim 1 or 2 which is a compound of formula I wherein
R_1 is chloro,
R_2 is hydrogen,
R_3 is trifluoromethyl and
R_4 is hydrogen.

4. A compound according to claim 1 or 2 which is a compound of formula I wherein
R_1 is chloro,
R_2 is hydrogen,
R_3 is trifluoromethyl and
R_4 is a group of formula $-CO-O-(CH_2)_2-N[(C_2H_5OH)(CH_3)]$.

5. A compound according to any one of claims 1 to 4 in the form of a salt.

6. Use of a compound of any one of claims 1 to 5 in the preparation of a medicament for the therapy of IgE-synthesis-mediated diseases, autoimmune diseases, gastrointestinal diseases and chronic rejection of transplants.

7. A method of treatment of IgE-synthesis-mediated diseases, autoimmune diseases, gastrointestinal diseases and chronic rejection of transplants which method comprises administering a therapeutically effective amount of a compound of any one of claims 1 to 5 to a subject in need of such treatment.

8. A compound of any one of claims 1 to 5 for use as a pharmaceutical.

9. A pharmaceutical composition comprising a compound of any one of claims 1 to 5 in association with at least one pharmaceutical excipient.

10. Use of an amine, which is substituted by
- phenyl-substituted pyrimidin; and
- phenyl; and
- a third substituent, e.g. R_4 as defined in claim 1 to 5,
in the preparation of a medicament for the treatment of IgE-synthesis-mediated diseases, autoimmune diseases, gastrointestinal diseases and chronic rejection of transplants.